Cochrane Library

Cochrane Database of Systematic Reviews

Piracetam for acute ischaemic stroke (Review)

Ricci S, Celani MG, Cantisani TA, Righetti E

Ricci S, Celani MG, Cantisani TA, Righetti E.
Piracetam for acute ischaemic stroke.
Cochrane Database of Systematic Reviews 2012, Issue 9. Art. No.: CD000419.
DOI: 10.1002/14651858.CD000419.pub3.

TABLE OF CONTENTS

[Intervention Review]

Piracetam for acute ischaemic stroke

Stefano Ricci[1], Maria Grazia Celani[2], Teresa Anna Cantisani[2], Enrico Righetti[3]

[1]UO Neurologia, ASL 1 dell' Umbria, Città di Castello, Italy. [2]Neurofisiopatologia, Azienda Ospedaliera Perugia, Perugia, Italy. [3]A USL 2 dell'Umbria, Stroke Unit, Ospedale di Città della Pieve, Città della Pieve, Italy

Contact address: Stefano Ricci, UO Neurologia, ASL 1 dell' Umbria, Ospedale, Via Engels, Città di Castello, 06012, Italy. istitaly@unipg.it.

Editorial group: Cochrane Stroke Group
Publication status and date: New search for studies and content updated (no change to conclusions), published in Issue 9, 2012.

Citation: Ricci S, Celani MG, Cantisani TA, Righetti E. Piracetam for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2012, Issue 9. Art. No.: CD000419. DOI: 10.1002/14651858.CD000419.pub3.

ABSTRACT

Background

Piracetam has neuroprotective and antithrombotic effects that may help to reduce death and disability in people with acute stroke. This is an update of a Cochrane Review first published in 1999, and previously updated in 2006 and 2009.

Objectives

To assess the effects of piracetam in acute, presumed ischaemic stroke.

Search methods

We searched the Cochrane Stroke Group Trials Register (last searched 15 May 2011), the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 2), MEDLINE (1966 to May 2011), EMBASE (1980 to May 2011), and ISI Science Citation Index (1981 to May 2011). We also contacted the manufacturer of piracetam to identify further published and unpublished studies.

Selection criteria

Randomised trials comparing piracetam with control, with at least mortality reported and entry to the trial within three days of stroke onset.

Data collection and analysis

Two review authors extracted data and assessed trial quality and this was checked by the other two review authors. We contacted study authors for missing information.

Main results

We included three trials involving 1002 patients, with one trial contributing 93% of the data. Participants' ages ranged from 40 to 85 years, and both sexes were equally represented. Piracetam was associated with a statistically non-significant increase in death at one month (approximately 31% increase, 95% confidence interval 81% increase to 5% reduction). This trend was no longer apparent in the large trial after correction for imbalance in stroke severity. Limited data showed no difference between the treatment and control groups for functional outcome, dependence or proportion of patients dead or dependent. Adverse effects were not reported.

Authors' conclusions

There is some suggestion (but no statistically significant result) of an unfavourable effect of piracetam on early death, but this may have been caused by baseline differences in stroke severity in the trials. There is not enough evidence to assess the effect of piracetam on dependence.

PLAIN LANGUAGE SUMMARY

Piracetam for acute ischaemic stroke

Ischaemic stroke is the third leading cause of death in developed countries, and the first leading cause of long-term disability in survivors. Piracetam is a drug which has been marketed by drug companies in several countries for many years as a 'nootropic' agent: a drug which has metabolic activity in the human brain. Experiments in animals suggest that piracetam could have beneficial effects in patients with acute stroke. The efficacy and safety of piracetam in patients with acute stroke have not yet been proven. There have been a number of randomised controlled trials of piracetam given to patients within 48 hours of the onset of their stroke. Data from three trials, involving 1002 patients, were available for this review, but almost all came from a single study. The data reviewed did not provide conclusive evidence about the effects of piracetam for acute stroke. One additional, large study has been conducted and interrupted by the manufacturer after some preliminary analyses were carried out, but the results have not been made available to the scientific community.

BACKGROUND

Ischaemic stroke is still the third leading cause of death in developed countries, and the first leading cause of long-term disability in survivors, but despite this there is still no pharmacological treatment of proven efficacy or with a favourable risk/benefit ratio for the acute phase of the disease (aspirin has been shown to be effective, but just as an early secondary prevention treatment).

Various strategies are currently being considered, in relation to both circulatory impairment (e.g. antithrombotics, thrombolytics) and neuroprotection of the ischaemic brain (e.g. N-methyl-D-aspartate (NMDA) blocking agents, sodium channel blockers). Piracetam is a drug which has been marketed by drug companies in several countries for many years as a 'nootropic' agent (a drug which has metabolic activity in the human brain), and for the treatment of myoclonus. A Cochrane Review has been published on the efficacy of piracetam for ameliorating language in aphasic stroke patients (Greener 2001); the drug has also been considered for acute stroke treatment (Noble 1996). The exact mechanism of action of piracetam is not known and several different effects (possibly as the result of an action on a very basic cell function) have been described: a neuroprotective effect (restoration of neurotransmission, improvement of metabolism) which is evident in the presence of hypoxia (Giurgea 1970; Schaffler 1988) and an antithrombotic effect (improvement of microcirculation, decrease of platelet aggregation) (Herrschaft 1978; Moriau 1993). The aim of this review is to verify whether the available evidence from controlled trials is in favour of a beneficial effect of piracetam in acute ischaemic stroke. The potential effects of piracetam in chronic stroke patients is dealt with in a separate review (Greener 2001)

This is an update of a Cochrane Review first published in 1999, and previously updated in 2006 and 2009.

OBJECTIVES

The objective of this review was to determine the effectiveness and safety of piracetam, given within three days of stroke onset to patients with acute ischaemic stroke, in whom computed tomography (CT) or magnetic resonance imaging (MRI) scanning has been performed to identify intracerebral haemorrhage. The main outcomes of interest were death from all causes and poor outcome (that is, death or dependence) at final follow-up.

We wished to test the following hypothesis: a policy of immediate piracetam therapy is associated with a reduced risk of being dead or dependent in activities of daily living at the end of the final follow-up (that is, a few months after stroke onset). We also wished to consider (where available) any evidence of the effect of piracetam on haemorrhagic stroke and to review the evidence, when available, on whether or not piracetam therapy increases the risk of fatal or disabling intracranial haemorrhage.

METHODS

Criteria for considering studies for this review

Types of studies

We identified all truly unconfounded randomised trials in which treatment with piracetam, given within approximately 48 hours from stroke onset, was compared with control in patients with presumed acute ischaemic stroke. We excluded trials without true randomisation.

Types of participants

Since this review focuses on acute stroke, we excluded trials in which patients commenced treatment more than three days from stroke onset. We have included studies that involved patients of any age and either sex.

Types of interventions

The only agent considered in this review was piracetam, given intravenously (iv) or orally, or both, at any dose, compared with placebo or open control.

Types of outcome measures

The main outcomes of interest were as follows.

1. Death from any cause at the end of the treatment period: this was the primary outcome.
2. Death from any cause at the end of trial follow-up.
3. Dependence from stroke at the end of trial follow-up (that is, the patient is dependent on help from other people in activities of daily living). If the results were expressed as scale scores (Rankin or Barthel scales), these were dichotomised into dependent/independent.
4. A combination of death or dependence at the end of trial follow-up.
5. Fatal and non-fatal intracranial haemorrhages at the end of the treatment period.
6. Any major extracranial haemorrhage (fatal or requiring transfusion) at the end of the treatment period.

Search methods for identification of studies

See the 'Specialized register' section in the Cochrane Stroke Group module published in *The Cochrane Library*. We searched for trials in all languages and arranged translation of relevant studies published in languages other than English or Italian.

Electronic searches

We searched the Cochrane Stroke Group Trials Register, which was last searched by the Managing Editor on 15 May 2011. In addition, we searched the Cochrane Central Register of Controlled Trials (CENTRAL) (*The Cochrane Library* 2011, Issue 2), MEDLINE (1966 to May 2011) (Appendix 1), EMBASE (1980 to may 2011) (Appendix 2), and ISI Science Citation Index (1981 to May 2011). We used the MEDLINE search strategy (Appendix 1) to search the Cochrane Central Register of Controlled Trials and modified it for the other databases.

Searching other resources

We contacted the manufacturer of piracetam (UCB) to identify further published and unpublished studies.

Data collection and analysis

Two review authors (SR and MGC) independently screened the titles and abstracts of the studies identified from the database searches and excluded obviously irrelevant articles. We obtained the full text of the remaining articles and the same two authors

independently selected studies meeting the inclusion criteria for the review. We resolved disagreement by discussion and consultation with other review authors. The same two review authors independently extracted the relevant data from each trial, including randomisation method, blinding, number of patients lost to follow up, and type of possible analysis (intention-to-treat or explanatory), and the other two review authors checked the results. We also considered the following details: the number of post-hoc exclusions, the number of patients included without a prior CT, and the number of patients randomised and analysed but not treated for whatever reason. When relevant information was not available from the publication, we tried to make direct contact with the trialists.

We tested heterogeneity between trials using a Chi^2 test, where $P \leq 0.05$ was taken to indicate significant heterogeneity. We also used I^2 statistics. As long as statistical heterogeneity did not exist for the outcome where it was calculated (early death), we calculated pooled odds ratios (OR) and 95% confidence intervals (CI) for all the analyses using the Peto fixed-effect model.

We considered the following sensitivity analyses:

1. all patients, and only patients with CT before randomisation;
2. effects of different doses and routes of administration;
3. all trials, and only blinded trials;
4. whether method of concealment of next treatment allocation was good or poor.

RESULTS

Description of studies

See 'Characteristics of included studies'.

Only three of the 19 available studies fulfilled the entry criteria. In fact, we excluded the study by Creytens (Creytens 1980) because there was no CT examination to allow stroke diagnosis and pathological subgroup diagnosis. All included trials used piracetam intravenously in the acute phase compared with placebo. The number of participants was 1002: ages ranged from 40 to 85 and both sexes were equally represented. In the largest trial (PASS 1997) the sex ratio was almost one. CT scans were carried out for all patients participating in the two small studies, whereas, CT scans were missing in seven patients in the PASS trial, and showed a haemorrhage in 31 patients (15 piracetam and 16 placebo) (PASS 1997). These patients were included in our analysis of the single study, as it was an intention-to-treat analysis. Posterior circulation strokes were excluded as well as patients with coma (Glasgow Coma Scale less than 4) or a mass effect with a midline shift on the early scan.

Overall, early case fatality was 18%. The time of treatment from onset of stroke varied between 12 hours to 'preceding three days'. Although this last description was a bit unclear, we decided to include this study because it is reasonable to assume that only very few, if any, patients were treated after 48 hours. Only one study used a measure of functional disability (PASS 1997). However, this was an ad hoc modification of the Barthel score. Original data have been provided to calculate dependence, defining dependence as patients scoring less than 85 on the Barthel index.

Risk of bias in included studies

We included three trials, which met our inclusion criteria, in the analysis and summarised them in the 'Characteristics of included studies' table. All were truly randomised, had adequate allocation concealment and were double blind. The reasons for excluding 16 trials from the analysis are summarised in the 'Characteristics of excluded studies' table. Information about the following aspects of trial quality that may relate to bias was not available from the examined trials:

1. any important imbalance in treatment groups;
2. the number of patients excluded from analysis.

Adverse events were not described in the trials; it was merely stated that there was no difference between the two groups.

Effects of interventions

The total number of individuals included in the three trials was 1002. For the outcome of death at one month, there was no evidence of statistical heterogeneity (Chi^2 3.09, df = 2, $P > 0.10$; $I^2 = 35\%$) even though 93% of the data came from one single trial (PASS 1997). The three trials showed a non-significant increase in the odds of early death (that is, at approximately one month) of 1.32 (95% CI 0.96 to 1.82) (Analysis 1.1); this result is almost completely based on data coming from the PASS study. However, the authors of this study controlled the possible imbalance of prognostic factors between the two groups with a logistic regression analysis. When differences in stroke severity were accounted for (214 patients in the treated group had an Orgogozo scale of less than 35, as compared to 195 in the placebo group) there was no correlation identified between the treatment group and mortality. Numbers of patients with haemorrhagic strokes or major extracranial haemorrhages were not available. Results on late death were only available for the PASS study, and were closely similar to those at one month (OR 1.32; 95% CI 0.97 to 1.80) (Analysis 1.2). Results on functional disability were only reported in the PASS study, using an ad hoc modified Barthel index. The manufacturer provided analysable disability data (460 and 463 patients; four excluded because of missing data): there was a modest, non-significant reduction in the odds of being dependent with piracetam (OR 0.90; 95% CI 0.67 to 1.20) (Analysis 2.1). When we considered poor prognosis (that is, death or dependence) there was no difference between treatment and control (OR 1.01; 95% CI 0.77 to 1.32) (Analysis 3.1). The planned sensitivity analyses were not possible because the required baseline data were not available or were not relevant.

DISCUSSION

The results of this review do not show any statistically significant effect of piracetam on early or late death. There was, however, an unfavourable trend toward early death in the PASS study, which accounted for 93% of the data. This may well be due to an imbalance in stroke severity between the two groups, as stated by the authors (PASS 1997). However, very severe patients were not included in this study and therefore the imbalance in severity is based on a difference in a neurological scale which, in itself, is not statistically significant.

The trend towards an increased risk of early death among piracetam-allocated patients is a concern. Post hoc subgroup

analysis of the PASS study (PASS 1997) suggests a benefit of very early piracetam use, a hypotheses which has been tested in PASS II (PASS II 1998). However, we cannot include these results in this systematic review because they have not been made available. We attempted to obtain data from the drug company which owns the interim results, but our request was refused.

We decided to exclude the Creytens study (Creytens 1980) because there was no CT examination to allow stroke diagnosis and pathological subgroup diagnosis. However, if we include early death data from this study (assuming a worst-case scenario whereby missing patients are recorded as dead) the overall result does not change. If we consider data on dependence, evaluated in only one study (PASS 1997), the odds ratio is in the opposite direction but it comes close to unity when considering death plus dependence. Patients with vertebrobasilar stroke were not included in any study, and this is a further limitation of these results.

It seems very unlikely that any further trial comparing piracetam with control, which seeks to establish the effect of this drug in acute stroke reliably, will now be conducted.

AUTHORS' CONCLUSIONS

Implications for practice

Trials of piracetam do not provide definite evidence of a beneficial or harmful effect on death in acute ischaemic stroke. The available data do not support the routine use of piracetam in the management of patients with acute ischaemic stroke.

Implications for research

If the data from PASS II were made available, it might be possible to reassess the need for further randomised controlled trials of this agent in acute stroke. However, for now, the available evidence does not suggest that further controlled trials of piracetam in acute stroke are justified.

ACKNOWLEDGEMENTS

We are grateful to the Cochrane Neurological Network and to the Chinese Cochrane Center for their help in translating the Chinese paper. UCB sent us data on the PASS study (PASS 1997).

REFERENCES

References to studies included in this review

Ming 1990 *{published data only}*

Ming A, Fritz V, Winterton R, Esser J, Hinton S. Piracetam versus placebo in first, acute, non-haemorrhagic, carotid territory stroke: a double-blind pilot study. Symposium Piracetam, Athens, Greece, 29 April 1990, pp 139-51.

PASS 1997 *{published and unpublished data}*

De Deyn P, De Reuck J, Deberdt W, Vlietnick R, Orgogozo J, for members of the Piracetam in Acute Stroke Study (PASS) Group. Treatment of acute ischemic stroke with piracetam. *Stroke* 1997;**28**:2347-52.

Platt 1993 *{published data only}*

Platt D, Horn J, Summa J, Shimitt-Ruth R, Kaunntz J, Kronert E. On the efficacy of piracetam in geriatric patients with acute cerebral ischemia: a clinical controlled double-blind study. *Archives of Gerontology and Geriatrics* 1993;**16**:149-64.

References to studies excluded from this review

Burd 1997 *{published data only}*

Burd GS, Gusev EI, Skvortsova VI, Konstantinova MV, Bolotov DA, Vanichkyn AV. The use of piracetam (nootropil) in acute hemispheric ischemic stroke (HIS). *European Journal of Neurology* 1997;**4 Suppl 1**:s51.

Creytens 1980 *{published data only}*

Creytens G. Some new approaches in the treatment of cerebral pathology. *Acta Therapeutica* 1980;**6**:33-53.

Garcia Pastor 2004 *{published data only}*

Garcia Pastor A, Diaz Otero F, Gill Lunez AC, Villanueva Osorio JA. Tolerability and efficacy of the combination of piracetam and citicoline in acute ischaemic stroke. A randomised comparative open study. *Stroke* 2004;**35**(6):e286.

Gusev 1997 *{published data only}*

Gusev EI, Burd GS, Jekht AB, Skwortsova VI, Selikhova MV, Pavlow NA, et al. The metabolic therapy of acute stroke: the use of nootropil. *Zhurnal Nevrologii I Psickhiatrii imenuii S.S. Korasakowa* 1997;**97**(10):24-8.

Herrschaft 1988 *{published data only}*

Herrshaft H. The effectiveness of piracetam in acute cerebral ischemia in man. *Medizinische Klinik* 1988;**83**:667-77.

Huo 2004 *{published data only}*

Huo Q. Qingkailing, naofukang and ligustrazine for acute ischemic stroke. *Shaanxi Journal of Traditional Chinese Medicine* 2004;**25**:151-2.

Karoutas 1990 *{published data only}*

Karoutas G. A randomised, double blind, placebo controlled study of piracetam in patients with acute ischaemic cerebral infarct in carotid territory. Symposium Piracetam. 1990:135-8.

Kartin 1979 *{published data only}*

Kartin P, Povse M, Skondia V. Clinical study of piracetam in patients with subacute cerebrovascular accidents. *Acta Therapeutica* 1979;**5**:235-43.

Kozubski 1998 *{published and unpublished data}*

Kozubski W. Comparison of piracetam vs dextran 40 in ischemic stroke in elderly patients. *European Journal of Neurology* 1995;**2 Suppl 2**:27.

* Kozubski W. Piracetam vs dextran 40 in acute ischaemic stroke in elderly patients [Porownanie skutecznosci piracetamu i dekstranu 40 tys. u chorych w podeszlym wieku z niedokrwiennym udarem mozgu]. *Wiadomosci Lekarskie* 1998;**51**(7-8):321-5.

Kozubski W. Piracetam vs dextran 40 in acute ischemic stroke in elderly patients - a single blind study. *Journal of Neurology* 1997;**244 Suppl 3**:s55.

Meng 2003 *{published data only}*

Meng QL, Geng JG. Ganglioside GM1 in treating acute cerebral infarction. *Chinese Journal of New Drugs and Clinical Remedies* 2003;**22**(1):19-21.

PASS II 1998 *{published and unpublished data}*

Orgogozo JM, De Reuck J, Van Vleymen B, for the PASS II Group. Piracetam Acute Stroke Study II (PASS II). *Cerebrovascular Diseases* 1998;**8 Suppl 4**:84.

Piradov 1992 *{published and unpublished data}*

Piradov M, Susline Z, Lebedeva N, Altunine M, Shchunkin J. Piracetam in acute ischaemic stroke. *Cerebrovascular Diseases* 1992;**2**:235.

Shan 2001 *{published data only}*

Shan P, Liu S, Chi Z. Effect of fluoxetine on treatment of post stroke depression. *Acta Academiae Medicinae Shandong* 2001;**39**(3):229-30.

Shi 1998 *{published data only}*

Shi FC, Wang YS, Zhou JC. Primary study of jiannaojiangzhi on treatment of 309 patients with cerebral infarction. *Chinese Journal of Practical Internal Medicine* 1998;**18**(6):348-9.

Tunali 1997 *{published data only}*

Tunali F, Ozalp K, Erdogan N, Ozge A, Misirli A, Erenoglu N. The value of piracetam on acute ischemic stroke. *European Journal of Neurology* 1997;**4 Suppl 1**:152.

Zhang 2002 *{published and unpublished data}*

Zhang L-L, Li H-Y, Li Y-Z. Citicoline capsules vs piracetam tablets in treatment of cerebral infarction. *Chinese Journal of New Drugs and Clinical Remedies* 2002;**21**:202-4. [MEDLINE: ISSN 1007-7669]

Additional references

Giurgea 1970

Giurgea C, Mouravieff-Lesuisse F, Leemans R. Electropharmacologic correlations in oxygen deficient anoxia of rabbits in natural or artificial respiration [Correlations electro-pharmacologiques au cours de l'anoxic oxyprive chez le lapin en respiration libre ou artificielle]. *Revue Neurologique (Paris)* 1970;**122**(6):484-6.

Greener 2001

Greener J, Enderby P, Whurr R. Pharmacological treatment for aphasia following stroke. *Cochrane Database of Systematic Reviews* 2001, Issue 4. [DOI: 10.1002/14651858.CD000424]

Herrschaft 1978

Herrschft H. The effect of piracetam on global and regional cerebral blood flow in acute cerebral ischemia of man. *Medizinische Klinik* 1978;**73**:195-202.

Moriau 1993

Moriau M, Crasborn L, Lavenne-Pardonge E. Platelet antiaggregant and rheological properties of piracetam: a pharmacodynamic study in normal subjects. *Arzneimittel-Forschung* 1993;**43**:110-8.

Noble 1996

Noble S, Benfield P. Piracetam: a review of its potential as a rehabilitative treatment after stroke. *CNS Drugs* 1996;**5**(6):1-12.

Schaffler 1988

Schaffler K, Klausnitzer W. Randomized placebo-controlled double-blind cross-over study on antihyoxidotic effects of piracetam using psychophysiological measures in healthy volunteers. *Arzneimittel-Forschung* 1988;**38**:288-91.

References to other published versions of this review

Ricci 1999

Ricci S, Celani MG, Cantisani TA, Righetti E. Piracetam for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 1999, Issue 2. [DOI: 10.1002/14651858.CD000419]

Ricci 2006

Ricci S, Celani MG, Cantisani TA, Righetti E. Piracetam for acute ischaemic stroke. *Cochrane Database of Systematic Reviews* 2006, Issue 2. [DOI: 10.1002/14651858.CD000419]

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Ming 1990

Methods	Parallel RCT 30 days follow-up Co-interventions (standard symptomatic treatment)
Participants	19 patients included Inclusion criteria: 40 to 80 years, within 48 hours, first ischaemic supratentorial stroke, GCS > 4
Interventions	Piracetam 12 g iv daily for 5 days, then 4.8 g orally daily for other 25 days versus placebo
Outcomes	Impairment scales (not analysed in this review) Death rate available from the study
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

PASS 1997

Methods	Parallel multicentre RCT Follow-up at 4 and 12 weeks Low-dose heparin allowed, full dose heparin allowed after 48 hours

PASS 1997 *(Continued)*

	ASA not recommended during the first 24 hours Thrombolysis, haemodilution, dipyridamole and ticlopidine forbidden
Participants	927 patients included Inclusion criteria: age 40 to 85, clinically supratentorial ischaemic stroke within 12 hours, arousable patients, no midline shift on CT, Orgogozo scale greater than 5 and less than 70
Interventions	Piracetam 12 g iv daily for 4 days then 12 g daily for 4 weeks orally, then 4.8 g daily orally for 8 weeks versus placebo
Outcomes	Orgogozo scale Modified Barthel scale Death rate available from the study, both at 4 and 12 weeks
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

Platt 1993

Methods	Parallel RCT 28 days follow-up Co-interventions (heparin 15000 U daily and haemodilution)
Participants	56 patients included Inclusion criteria: above 65 years, with supratentorial first ischaemic stroke within preceding 3 days (exact time not clearly stated) Exclusion criteria included cerebral oedema and contraindication of hypervolaemic haemodilution
Interventions	Piracetam 12 g iv daily for 2 weeks and then 4.8 g orally daily for 2 weeks versus placebo
Outcomes	Cerebral flow measured by SPECT and motor neurological scales (not analysed in this review) Death rates available in the text
Notes	More women were randomised to piracetam than to placebo 2 patients in the piracetam group had a haemorrhagic stroke

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment (selection bias)	Low risk	A - Adequate

ASA: acetylsalicylic acid (aspirin)
CT: computed tomography
GCS: Glasgow Coma Scale
iv: intravenous
RCT: randomised controlled trial
SPECT: Single Photon Emission Computed Tomography

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Burd 1997	The study appears not to be randomised. We wrote to the authors for clarification but have not received a reply
Creytens 1980	There is no CT diagnosis of the possible cerebral ischaemia, therefore haemorrhages or cerebral neoplasms cannot be ruled out. Time to randomisation was not stated. No more information from UCB Pharma (the manufacturer) is available
Garcia Pastor 2004	The study compares piracetam to citicoline and to the combination of the 2 drugs in 70 patients with acute ischaemic stroke. There is no control group
Gusev 1997	This is a non-randomised comparative study
Herrschaft 1988	Patients included up to 5 days after their stroke. No data on mortality are available
Huo 2004	There is no control group, but piracetam + ligustrazine are compared with a Chinese drug
Karoutas 1990	No definition of the time interval from the event to inclusion. No data on mortality are available
Kartin 1979	Time interval from the ischaemic cerebral event to inclusion was 2 weeks. Patients were selected and not randomised
Kozubski 1998	In this study 47 acute stroke patients were randomly allocated to piracetam plus dextran versus dextran. There was no control group
Meng 2003	This study compares piracetam or citicoline to GM1. There is no control group
PASS II 1998	This study was interrupted by the sponsor after a futility analysis. No results were made available to the scientific community. Our requests for data, made both to the main investigator and the sponsor, were unsuccessful
Piradov 1992	Only patients who completed the treatment were analysed. When a patient stopped the treatment for any reason, a new patient was enrolled into the study as a substitute. Randomisation procedure not stated
Shan 2001	This study is not of acute stroke patients, but is about post-stroke depression
Shi 1998	There is no information on case-fatality rate, nor on follow-up after 30 days
Tunali 1997	It is not clear from the study whether and how the study was randomised. No information from the authors was available
Zhang 2002	Time interval is not stated in the English version of the paper. Information in the original Chinese version was requested from the Chinese Cochrane Center. The study compares piracetam to citicoline, but the time interval was not clearly defined in the reply

CT: computed tomography

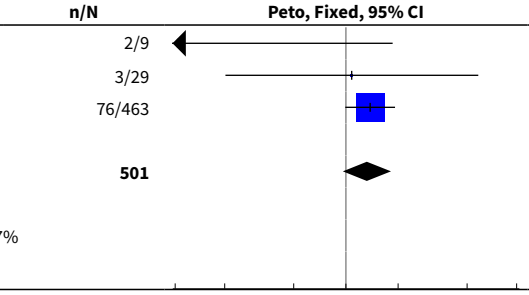
DATA AND ANALYSES

Comparison 1. Piracetam versus control

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death at approximately 1 month	3	1002	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.96, 1.82]
2 Death at 12 weeks	1	927	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.32 [0.97, 1.80]

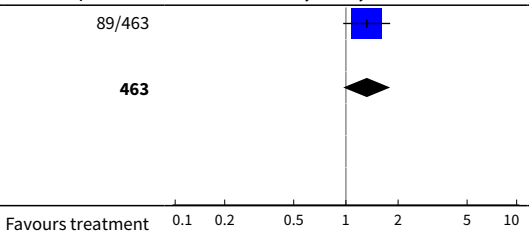
Analysis 1.1. Comparison 1 Piracetam versus control, Outcome 1 Death at approximately 1 month.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
Ming 1990	0/10	2/9		1.26%	0.11[0.01,1.86]
Platt 1993	3/27	3/29		3.65%	1.08[0.2,5.8]
PASS 1997	99/464	76/463		95.09%	1.38[0.99,1.92]
Total (95% CI)	**501**	**501**		**100%**	**1.32[0.96,1.82]**
Total events: 102 (Treatment), 81 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.09, df=2(P=0.21); I^2=35.37%					
Test for overall effect: Z=1.71(P=0.09)					



Analysis 1.2. Comparison 1 Piracetam versus control, Outcome 2 Death at 12 weeks.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
PASS 1997	111/464	89/463		100%	1.32[0.97,1.8]
Total (95% CI)	**464**	**463**		**100%**	**1.32[0.97,1.8]**
Total events: 111 (Treatment), 89 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.74(P=0.08)					



Comparison 2. Dependence at 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Dependence at 12 weeks	1	723	Peto Odds Ratio (Peto, Fixed, 95% CI)	0.90 [0.67, 1.20]

Analysis 2.1. Comparison 2 Dependence at 12 weeks, Outcome 1 Dependence at 12 weeks.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
PASS 1997	182/349	205/374		100%	0.9[0.67,1.2]
Total (95% CI)	**349**	**374**		**100%**	**0.9[0.67,1.2]**
Total events: 182 (Treatment), 205 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.72(P=0.47)					

Comparison 3. Death or dependence at 12 weeks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Death or dependence at 12 weeks	1	923	Peto Odds Ratio (Peto, Fixed, 95% CI)	1.01 [0.77, 1.32]

Analysis 3.1. Comparison 3 Death or dependence at 12 weeks, Outcome 1 Death or dependence at 12 weeks.

Study or subgroup	Treatment n/N	Control n/N	Peto Odds Ratio Peto, Fixed, 95% CI	Weight	Peto Odds Ratio Peto, Fixed, 95% CI
PASS 1997	293/460	294/463		100%	1.01[0.77,1.32]
Total (95% CI)	**460**	**463**		**100%**	**1.01[0.77,1.32]**
Total events: 293 (Treatment), 294 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.06(P=0.95)					

APPENDICES

Appendix 1. MEDLINE search strategy

MEDLINE (Ovid)

1. cerebrovascular disorders/ or basal ganglia cerebrovascular disease/ or exp brain ischemia/ or carotid artery diseases/ or carotid artery thrombosis/ or intracranial arterial diseases/ or cerebral arterial diseases/ or exp "intracranial embolism and thrombosis"/ or exp stroke/
2. (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or transient isch?emic attack$ or tia$).tw.
3. (brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation).tw.
4. (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$).tw.
5. 3 and 4
6. 1 or 2 or 5
7. Piracetam/
8. (piracetam or nootropil or nootropyl or pirazetam or pyramem or UCB-6215 or 2-pyrrolidone-n-acetamide).tw.
9. 7 or 8
10. 6 and 9

Appendix 2. EMBASE search strategy

EMBASE (Ovid)

1. cerebrovascular disease/ or cerebral artery disease/ or cerebrovascular accident/ or stroke/ or vertebrobasilar insufficiency/ or carotid artery disease/ or exp carotid artery obstruction/ or exp brain infarction/ or exp brain ischemia/ or exp occlusive cerebrovascular disease/ or stroke patient/
2. (stroke$ or apoplex$ or cerebral vasc$ or cerebrovasc$ or cva or transient isch?emic attack$ or tia$).tw.
3. (brain or cerebr$ or cerebell$ or vertebrobasil$ or hemispher$ or intracran$ or intracerebral or infratentorial or supratentorial or middle cerebr$ or mca$ or anterior circulation).tw.
4. (isch?emi$ or infarct$ or thrombo$ or emboli$ or occlus$ or hypoxi$).tw.
5. 3 and 4
6. 1 or 2 or 5
7. Piracetam/
8. (piracetam or nootropil or nootropyl or pirazetam or pyramem or UCB- 6215 or 2-pyrrolidone-n-acetamide).tw.
9. 7 or 8
10. 6 and 9

FEEDBACK

Comment

Summary

The reviewer has given the impression that a related Cochrane protocol (Greener, Enderby and Whurr: Pharmacological treatment for aphasia following stroke) will only include patients with long-term post-stroke aphasia, and will include disability as an outcome measure. The proposed review will in fact cover patients with aphasia at any time after their stroke, and will only look at aphasia as an outcome measure.

Reply

Ms Greener is right since her review of piracetam for stroke will cover the treatment of aphasia at any time after stroke while our review deals with the effects of piracetam on functional outcome when given during the acute phase of stroke.

Contributors

Comment: Jenny Greener
Reply: Stefano Ricci

WHAT'S NEW

Date	Event	Description
28 May 2012	New citation required but conclusions have not changed	The conclusions have not changed.
18 May 2011	New search has been performed	We have updated the searches to 15 May 2011. We did not identify any new relevant trials.

HISTORY

Protocol first published: Issue 3, 1997
Review first published: Issue 2, 1999

Date	Event	Description
30 September 2008	Amended	Converted to new review format.
7 November 2005	New search has been performed	We found no new relevant information up to June 2005. We requested information on two trials (Burd 1997; Tunali 1997) in

Date	Event	Description
		a standardised format but have received no response from the study authors, possibly because these data are very old and the authors may have changed address. The PASS II study (PASS II 1998) was interrupted based on the results of a futility analysis. We requested data from the manufacturer but the answer was negative.

CONTRIBUTIONS OF AUTHORS

S Ricci and MG Celani extracted data from the original trials and prepared a summary; this summary was discussed with E Righetti and TA Cantisani, and a final agreement reached. The final revision was written according to this agreement by all the authors.

DECLARATIONS OF INTEREST

None known.

INDEX TERMS

Medical Subject Headings (MeSH)

Acute Disease; Brain Ischemia [*drug therapy] [mortality]; Fibrinolytic Agents [adverse effects] [*therapeutic use]; Neuroprotective Agents [adverse effects] [*therapeutic use]; Piracetam [adverse effects] [*therapeutic use]; Randomized Controlled Trials as Topic; Stroke [*drug therapy] [mortality]; Treatment Outcome

MeSH check words

Humans